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NUTRITION IN THE AGE-RELATED DISABLEMENT PROCESS

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Abstract: The transition from independence to disability in older adults is characterized by detectable changes in body composition and physical function. Epidemiologic studies have shown that weight loss, reduced caloric intake and the reduced intake of specific nutrients are associated with such changes. The mechanisms underlying these associations remain unclear, and different hypotheses have been suggested, including the reduction of the antioxidant effects of some nutrients. Changes in muscle mass and quality might play a central role in the pathway linking malnutrition, its biological and molecular consequences, and function. A different approach aims at assessing diets by dietary patterns, which capture intercorrelations of nutrients within a diet, rather than by selective foods or nutrients: epidemiologic evidence suggests that some types of diet, such as the Mediterranean diet, might prevent negative functional outcomes in older adults. However, despite a theoretical and empirical basis, intervention studies using nutritional supplementation have shown inconclusive results in preventing functional impairment and disability. The present work is the result of a review and consensus effort of a European task force on nutrition in the elderly, promoted by the International Association of Gerontology and Geriatrics (IAGG) European Region. After the critical review of different aspects related to the role of nutrition in the transition from independence to disability, we propose future lines for research, including the determination of levels of inadequacy and target doses of supplements, the study of interactions (between nutrients within a diet and with other lifestyle aspects), and the association with functional outcomes.

Key words: Disability, frailty, muscle, sarcopenia, nutrition/diet.

Introduction

Poor health and loss of independence are not inevitable consequences of aging. During the aging process, modifiable risk factors, such as an inadequate diet and physical inactivity, interact with genes and environmental factors to determine a reduction of physiologic reserve of different organs and systems. This reduction increases the risk of chronic diseases and disability. Understanding the contribution of these potentially modifiable risk factors may help to develop intervention strategies aimed at improving health and maintaining independence in older adults (1). The International Association of Gerontology and Geriatrics (IAGG), European Region, created this established interest group on nutrition and aging, with the primary aim of suggesting gaps in knowledge and future lines of research on this topic. The present one is the first of a three papers series, and aims to discuss the role of diet and nutrients in the prevention or postponement of disability. The second paper will address the issue of screening and assessment of malnutrition, and the third one will focus on interventions to prevent and possibly treat malnutrition in elderly people.

In this article, we will specifically focus on muscle's structural and functional changes associated with aging as a potential mediator of the relationship between nutrition and disability, and will dedicate a short mention to cognitive function. Finally, we will comment on important gaps in current knowledge and propose lines for future research on this topic.

Epidemiology of poor nutrition in older community dwellers

Dietary quality and adequacy

The dietary intake of foods and nutrients are highly related, and, as people do not eat single nutrients or foods, evaluating the effects of overall diet through dietary pattern analysis has attracted considerable interest in nutritional epidemiology. Assessing dietary quality, expressed by dietary intake of energy and nutrients, using dietary patterns analysis has the main

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advantage of capturing the strong interconnections of nutrients within a diet, as well as integrating complex interactive effects of many dietary exposures (2). To get insight in these patterns two statistical approaches are used: theoretical, 'a priori' methods based on current nutritional knowledge, and empirical, 'a posteriori' methods. An example of an 'a priori' approach is the Mediterranean Diet Score (MDS) (3). This score rates the degree of adherence of the observed diet with a Mediterranean type of diet, which has been associated with beneficial effects on mortality (4), demonstrating a good consistency with similar scores (5). Recent studies have shown that a higher MDS (higher adherence) is significantly associated with a reduced risk of all-cause mortality, cardiovascular diseases and cancer, with a reduced incidence of Parkinson's and Alzheimer disease (AD) (6), and a lower incidence of stroke (7), although this last outcome was investigated in a cohort of only women. Mechanisms involved in these protective effects of the Mediterranean diet pattern have been investigated. Adherence to Mediterranean diet pattern was cross-sectionally associated with a lower risk of metabolic syndrome (8). In a cohort study, higher MDS was shown to be associated with smaller age-related changes in blood pressure, suggesting that the Mediterranean diet pattern might reduce the incidence of hypertension (9). Studies into the mechanisms underlying these effects reported a blunted inflammatory response (10). Furthermore, a robust inverse association between the MDS and oxidative stress, independent of known cardiovascular disease risk factors or familial and genetic background was demonstrated (11). It has been questioned how each of the individual components of the diet contributes to the global observed beneficial effects: key factors appeared to be above median intakes of vegetables, fruits, cereals, and fish, below median intakes of saturated fat, with a high ratio of unsaturated to saturated lipids being particularly important, as well as moderate alcohol consumption (4, 5, 12). Several other studies demonstrated an association between 'a posteriori' extracted dietary patterns characterized by a high consumption of plant based foods (fruits, vegetables, and vegetable oils) with overall survival among older adults (13). From a public health perspective it is noteworthy that, unfortunately, adherence to these types of diet is decreasing in younger cohorts, while it tends to be higher in the elderly. For example, data from the EPIC-Elderly cohort study (4), reported that the prevalence of the highest MDS progressively increased from 25.9% in the 60-64 age group to 49.7% in people >75 years old. These trends are likely explained by cohort effects and secular trends, suggesting that the adherence to the Mediterranean diet would dramatically decrease in the near future.

Along with dietary quality, dietary adequacy (amounts of nutrients and energy intake in line with recommendations) plays an important role at older ages, as nutrition deficits are found to be associated with functional decline (14). In old age, nutritional inadequacies are widespread (15). Several studies have reported specific nutritional concerns in old age, including a high prevalence of vitamin D and vitamin B12 deficiency (16).

Risk factors and pathophysiology of decreased food intake in older community-dwellers

Dietary inadequacy might emerge from poor intakes, as observed in 7-21% of older adults in the United States (17).

A constellation of physiological and pathological changes associated with aging can substantially modify dietary preferences and intake and lead to specific nutritional deficits. The most relevant age-associated changes involved in nutritional problems encompass alterations in taste and smell, swallowing disorders, impaired esophageal peristalsis, decreased transpyloric flaws and delayed gastric emptying, increased activity of cholecystokinin (CCK), mild achlorhydria resulting from atrophic gastritis, increased colon transit times, lower anal squeeze pressures, silent aspiration and pneumonia, postprandial hypotension, constipation, fecal incontinence and diverticula (18). Impaired absorption of some micronutrients and minerals, especially vitamins B12 and D, as well as calcium and iron, mainly due to achlorhydria, has also been described (19). Hormones (e.g. leptin), neurotransmitters (e.g. opioids) and cytokines may also play a role. Loss of appetite, referred to as physiological anorexia of ageing, may predispose to protein and energy undernutrition (20).

Other risk factors for malnutrition are highly prevalent in old ages, and include dementia, depression, decreased visual acuity, poor dentition and pain from acute or chronic diseases, especially cancer. Commonly used medications (e.g. laxatives, corticosteroids, digoxin) may affect energy intake and appetite. Lastly, social factors that may accompany ageing (isolation, poverty, loss of spouse and alcoholism) may also contribute to reduced food intake (21).

Ageing is also accompanied by significant changes in body composition as fat increases by almost 50% at the expense of lean body mass (and especially loss of muscle mass) in both genders. This leads to a decrease in basal metabolic rate by about 2% per decade (22). Moreover, physical activity usually declines and so does total energy expenditure (23). Despite these changes, the demands for most vitamins, minerals and trace elements are not or only slightly reduced (25). Therefore, in order to avoid deficiency in specific nutrients, it is important that older persons eat foods that have a high nutrient density (18), to compensate for reduced food intakes.

Functional consequences of poor nutrition

Nutrition, physical performance, frailty and disability

Undernutrition is associated with different negative functional outcomes in the elderly. These include disability, functional limitations, and frailty, a state of reduced physiologic reserve of different systems determining a consequent high vulnerability to incident disability (24-26). Independent of energy intake, low intake of protein, vitamins D, E, C, and folate is associated with Fried et al.'s operational definition of frailty, which represents a constellation of signs and symptoms (unexplained weight loss, reduced grip strength, self-reported exhaustion, slow walking speed and low physical activity) associated with changes in body composition and impaired physical functioning (27). Vitamin D deficiency is associated with poor functional performance and falls (28). Low dietary intake of specific antioxidants and low levels of vitamin E are also associated with reduced physical performance and muscle strength (29). In the Women's Health and Aging Studies I and II, low levels of serum carotenoids independently predicted subsequent rises in interleukin-6 (IL-6), a marker of inflammation (30). In the same study, low levels of carotenoids were risk factors for the development of frailty (31) and severe walking disability (32), and low concentrations of vitamin B6, vitamin B12 and selenium (which exerts antioxidant properties) were predictors of activities of daily living (ADL) disability during three years of follow-up (33). Longitudinal data from the InChianti study showed that a low concentration of serum vitamin E, among other micronutrients, was associated with a subsequent decline in physical function (34).

Sarcopenia, a potential mediator

Muscle impairment seems a relevant step in the pathway linking poor nutrition to functional decline in the elderly. From age 70 onwards, about 1% of skeletal muscle mass per year is lost (35). This process is called sarcopenia. Muscle quality shows an even greater deterioration: in excess of mass decline, muscle strength decreases of about 3% every year and fat infiltration within muscle fibers increases (36). Not surprisingly, in older adults muscle strength and quality (fat infiltration etc.) appears more strongly associated with functional limitations, disability and mortality than muscle mass (37, 38). The amount of visceral, inter- and intramuscular fat continues to increase well into very old age (39), while subcutaneous fat first increases and later decreases with aging (40). Body fat in older persons is often a more important determinant of physical dysfunction compared to muscle mass, and, compared to muscle strength, seems more strongly associated with physical functioning (37, 41). The coexistence of high body fat with low muscle mass or strength is called sarcopenic obesity, which has been associated with incident disability (42).

The table 1 summarizes the evidence from recent studies looking at the effect of proteins, vitamin D, magnesium and antioxidants on muscle mass and function.

Oxidative stress, antioxidants, muscle and physical function

Dietary patterns characterized by high consumption of fruit and vegetables, which are rich in antioxidants, are associated with reduced markers of inflammation and of endothelial dysfunction (51). Adherence to the Mediterranean diet is associated with lower circulating levels of inflammatory markers, such as C-reactive protein, IL-6, and fibrinogen (52). Evidence from randomized clinical trials shows that Mediterranean diet reduces low density lipoprotein (LDL) oxidation in persons at high cardiovascular risk (53). Higher levels of inflammatory markers have potentially negative consequences, since they increase the risk of decline of muscle strength (54) and muscle mass (45).

Table 1
Associations of specific dietary factors with muscle mass and function

Dietary factor	Evidence	Some open questions
Proteins	• Inadequate intake may accelerate the loss of lean mass (43) • Protein anabolism can be stimulated by increased essential amino acid availability (44)	• Potential attenuation of the loss of lean mass with higher protein intakes? • Optimal level and type of proteins?
Vitamin D	• Low serum vitamin D has been associated with poor and decreasing muscle strength (45) • Vitamin D supplementation trial showed a substantial increase in quadriceps strength and functional performance in older persons (46)	• Observational studies are inconsistent (47)
Magnesium	• Low serum magnesium has been associated with reduced muscle strength (48)	
Carotenoids	• Low serum carotenoids have been associated with poorer muscle strength in older adults (49)	
Selenium	• Low plasma selenium has been associated with poorer muscle strength in older adults (50)	

Taken together, these results suggest that oxidative stress and inflammatory markers may mediate, at least in part, the relationship between nutrition and function in the elderly. The protective effect of antioxidants is attributed to their capacity to minimize the cellular damage by donating electrons and neutralizing reactive oxygen species (ROS) in order to maintain normal cellular physiology. Thus, dietary antioxidants may tip the balance between endogen antioxidants and oxidants and reduce, in turn, oxidative stress and injury (55), which may lead to neuronal or muscle damage and wasting (56, 57).

Other potential mechanisms explaining the association of nutrients with muscle and function

Undernutrition may contribute to frailty and decline in physical function through other mechanisms. For example, a low intake of energy may be associated with reduced efficiency of mitochondria because of the reduced proficiency of energy production in the aerobic metabolism. This may result in reduced "mechanical work" and increased sense of fatigue, leading to reductions in endurance and physical function (58). Furthermore, protein intake is necessary to counteract protein degradation in favor of protein synthesis (59) which is essential for the maintenance of muscle mass and strength (60). Deficiency of vitamin B-complex may lead to megaloblastic anemia (61), which is characterized by symptoms such as fatigue and weakness.

Nutrition and cognitive function

Vitamins (especially B6, B12 and folate), trace minerals and dietary lipids can affect the risk of cognitive decline and dementia, especially in frail older adults (62), although the evidence on the relation between B-vitamins and cognitive functioning and decline is inconclusive. Some studies have shown an association between low levels of either vitamin B12, or folate, or high homocysteine and the risk of developing AD (63). The intake of polyunsaturated fatty acids has been associated with cognitive decline (64). Finally, low levels of anti-oxidants, and in particular low levels of vitamin E, might expose to a higher risk of cognitive decline and dementia (65). Cognitive dysfunction, in turn, might be associated with reduced physical functioning (66), representing a further potential contributor to negative functional outcomes. Conversely, the dietary consumption of fruits and or vegetables seems protective against cognitive decline (62).

Intervention studies

Evidence from intervention studies is important to possibly support causal hypotheses suggested by observational studies. Different studies (well summarized in a recent meta-analysis (67)) assessed the effects of increased energy and protein intake on nutritional status or on intermediate outcomes (body composition measures, inflammation or other biological markers). Almost all quoted studies included functional outcomes only as secondary outcomes, reporting in general inconclusive results. Positive results were observed in few studies enrolling more selected populations (for example participants with higher risk of undernutrition or after hospital discharge or institutionalized) (67-70). Vitamin D has shown promising results on muscle strength and falls (71), besides the more intuitive beneficial effect on bone and the prevention of fractures. Few negative data are available on antioxidants, such as vitamin E (72), although observational studies showed a strong inverse correlation between their concentration and decline in physical performance and frailty. Studies using supplementation with these nutrients have mostly evaluated their effect on cognitive function, in general with disappointing results. To our best knowledge, no intervention study investigated the effect of omega-3 or other nutrients on functional outcomes in the general population.

Gaps in knowledge and future research

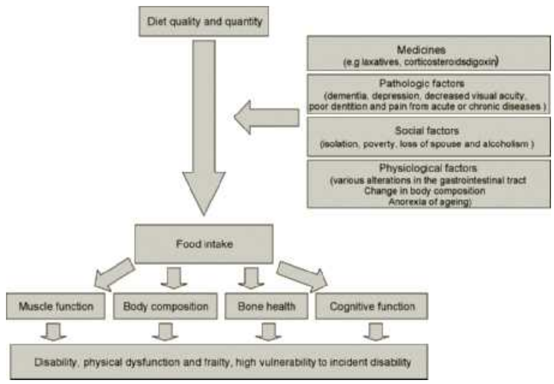
From the evidence summarized in the previous paragraphs, it is evident that more observational and intervention studies are needed to clarify the relationship between nutrition and functional outcomes. Main limitations and recommendations for future research, detailed in the following paragraph, are also resumed in the Table 2.

Although epidemiologic studies have shown interesting correlations between the levels of different nutrients and functional outcomes, this did not translate in successful results when nutrients replacement interventions were tested. In general, it is important to take into account that the interpretation of results on nutritional supplementation is complicated by several factors, such as the dose of micronutrients that likely ranges from physiological to mega doses, the presence of different nutrients in the supplements, the fact that older adults tend to reduce dietary intake during supplementation (73), and the characteristics of the group that has been targeted for supplementation. Furthermore, as we have previously underlined, people don't eat single nutrients or foods, but meals, and this could possibly explain part of the negative results, since the complex synergistic effect of the different nutrients has not been taken into account. Although studies on single nutrients might be easier to run because of a relatively simple design, studies examining dietary patterns are needed. In particular, no study so far has assessed the impact of diet on physical performance decline in older adults.

Table 2
Summary of main limitations of the published studies and possible, related, recommendations for future research

Main limitations	Possible recommendations
Intake data	
Data on levels of inadequate nutrient levels are scarce Levels of inadequacy, and range and target dose of supplements are not clearly defined Dietary intake during supplementation should be measured, as older adults tend to reduce intakes	More studies are needed to define micro-nutrient requirements and inadequacy in the elderly
Studies generally do not consider interactions between:	
• dietary nutrients	More observational and intervention studies examining dietary patterns and "real world" situations (diet, not nutrients) are needed
• diet and other age-related changes (e.g. inflammation)	Other physiological age-related processes need to be taken into account
• diet and other lifestyle factors (e.g. physical activity and exercise)	Look for interactions, and design combined interventions
Health outcome	
Outcomes are often intermediate (e.g. changes in nutritional or anthropometric parameters) and not strong clinical events (e.g. disability)	Select appropriate final functional outcomes (e.g. objective measures of physical performance)
Long term exposure might be needed to observe chronic and progressive processes (selected as outcomes)	Studies with appropriate follow-up and assessing midlife exposure need to be designed
Cause-effect relationships remain often controversial	Study dose-response effects
Outcomes tend to cluster (e.g. muscle, bone and cognition changes in relation to vit. D deficit)	
Pathways are still unclear	More research on nutrition and sarcopenia is needed (given the possible central role of the muscle mass and quality)
Interventions design	
Samples often not adequately selected (samples with increased risk might benefit the most)	Select specific populations (e.g. frail, using specific inclusion criteria or performance measures) for observational and/or intervention studies
Functional decline is often multifactorial in older adults	Multifactorial interventions should be designed
Low compliance might affect the results of interventions	Behavioural strategies in lifestyle modifications should be implemented

Figure
Possible pathways linking nutrition and diet with frailty and disability



Nutrition also seems to interact with different changes, involving multiple physiologic systems, during the aging process (for example antioxidants and inflammation), and with other behavioral risk factors, such as physical activity and exercise. The multifactorial contribution to functional decline associated with aging should be taken into account when studying the effects of nutrition.

Long term effect of the exposure could be more relevant or have a different impact on aging and its functional consequences than late life exposure. We found that studies on midlife exposure to diet and nutrients, which are obviously limited by complexity and costs, are lacking. Causal relationships would be also reinforced by the demonstration of dose-response effects between nutrients and health outcomes. Promising results of both observational and intervention studies have been shown with vitamin D. However, different individual studies have assessed the impact of vitamin D deficiency on different outcomes (muscle, bone, cognitive functions), which are interrelated and tend to cluster. This aspect should be possibly considered in future research studies. Also, levels of inadequacy of vitamin D and several other nutrients are still unclear.

Mechanistic studies, basic and experimental studies, targeted for example on antioxidants, should support and provide hypotheses for epidemiologic studies. The identification of possible causal pathways through epidemiological studies should help to inform the development of intervention studies. Future randomized clinical trials should mimic "real world" situations, considering the impact of diets more than single nutrients. Since better results have been shown on selected populations, targeted interventions should apply good inclusion criteria to select more frail subgroups. For example, measures of physical performance (74), as well as the clinical operational definition of frailty, such as the one provided by the Cardiovascular Health Study investigators (27), might be interesting instruments in this sense. Appropriate primary outcomes, such as objective measures of physical performance should be considered, since functional outcomes have been usually explored as secondary outcomes, whereas intermediate outcomes, such as nutritional or anthropometric parameters (nutrient levels, weight, body mass index, etc) were the primary outcomes. Follow up should have an appropriate duration, considering that chronic and progressive processes are "slow". Also, studies on specific areas, such as sarcopenia, need to be implemented. Considering the multifactorial etiology of age-related functional decline, multifactorial interventions (i.e. combining diet with exercise) might provide better results.

Finally, compliance problems might bias the studies' results (75). Despite the fact that lifestyle (including smoking, sedentary lifestyle, etc.) is an important risk factor for adverse health outcomes at all ages, and that interventions directed to modify these factors are beneficial for health, lifestyle modification remains a major public health challenge, and more behavioral studies are needed to investigate attitudes and lifestyles, and find strategies to modify them.

Conclusions

Inadequate diet and nutrition might represent a relevant, modifiable risk factor for functional decline and the transition to disability. More research is needed, especially solid intervention studies, to clarify basic aspects of the impact of nutrition on these outcomes and to finally generate the knowledge that will be translated to evidence-based dietary recommendations for the community of older adults.

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